REMARKS

Applicants thank the Examiner for the interview held on January 24, 2006. Applicants note that the following pending claims are, in view of the present office action, free of the prior art: 1-11, 13, 18, 20-21, 28, 40, 98-108 and 118.

Amendments to the Claims

Amendments to the claims are made solely to expedite prosecution. Applicants reserve the right to pursue the claims as originally filed and originally presented in this or future applications.

Claims 98, 105, and 118 have been canceled without prejudice. The matter of these claims is incorporated into independent claims 21, 28 and 43, respectively.

Claim 43 is amended to recite chimeric nucleases that comprise a nuclear localization signal, thus incorporating claim 118. The claim is also amended to correct an obvious error and recite a nucleic acid encoding a chimeric nuclease, not a chimeric nucleic acid.

Claim 114 is amended to include the article "the" which was previously omitted.

New claims 124 and 125 are specifically supported on pages 6 (lines 3-7), 8 (lines 23-26), 9 (lines 17-21), the paragraph spanning pages 33-34, and page 47 (lines 7-14) of the specification.

New claim 126 is supported, for example, on page 52 (lines 12-15 and 25-28).

No new matter has been introduced.

Amendments to the Specification

The Examiner has rejected the specification for the recitations "in bold" on pages 16 and 53 made in reference to Figure 4 in which it was stated that no boldface type was visible. Applicants have eliminated this language in the specification so that no reference is made to boldface type in Figure 4.

The Examiner has also brought to the Applicants attention an error in a description of Figure 2E on page 47, lines 12-13. Applicants have corrected the error in the figure description so that the relative rates of DSB-GT attributed to each promoter match the relative rates depicted in Figure 2E.

Applicants have also noted and corrected obvious errors in the specification on pages 13, 14, 17, 46, 51, 53, and 55. In each instance, the correct meaning is obvious from the context. In particular, the changes on pages 13, 14, and the paragraph spanning pages 46-47 are clear from Figures 1B, 1C, and 2E, respectively.

Claim Rejections

35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 98 and 105 under 35 U.S.C. § 112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

The Applicants have canceled claims 98 and 105 without prejudice, making the rejection moot.

35 U.S.C. § 112, first paragraph, enablement

The Examiner has also rejected claims 1-11, 13, 18, 20-21, 28, 40, 43, and 98-123 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement because the claims contain subject matter "which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." The Examiner also states "[a]pparently all of the examples shown in the specification use zinc finger for the binding domain, the nuclease cleavage domain of FokI and do not have a nuclear localization signal..." The Examiner further states that "[t]he instant claims have no limitation on the chimeric nucleases but are broadly drawn" to include a DNA binding domain, a cleavage domain, and a nuclear localization signal, and that "[i]t is not seen where in the specification it is taught that a nuclear localization signal is present in the chimeric nucleases made."

The Applicants respectfully disagree. The Examiner points out that Applicants teach a chimeric nuclease comprising a zinc finger DNA-binding domain and the endonuclease domain of FokI (page 3, lines 3-5 of the office action). However the present disclosure further describes chimeric nucleases generally comprising "one or more specific DNA-binding domains and one or more "cleavage" domains" (pg. 21, lines 15-16). Beginning on page 22, line 19 of the specification, the Applicants describe chimeric nucleases that combine DNA-binding domains from several different sources, both synthetic and natural, and specifically state that any DNA binding domain may be employed (page 21, lines 20-21). Likewise, any cleavage domain capable of conferring double-strand break activity is taught in the disclosure (page 21, particularly at lines 23-25); many specific examples are provided. Applicants have employed zinc finger DNA-binding domains and the FokI cleavage domain merely to provide an example of reduction to practice. It is improper to limit the scope of the claims to the working examples only. The application provides description for those forms of chimeric nucleases that are reduced to practice, as well as other forms that, in view of the disclosure, may be practiced by one of ordinary skill in the art without undue experimentation. DNA binding domains are highly modular and are known to function properly in a variety of fusion proteins, including, for example, the chimeric nucleases described in Kim et al. (1998) Biol Chem 379: 489-495 (Reference CU of IDS mailed on February 13, 2004); Kim et al. (1997) PNAS 94: 12875-12879 (Reference CT45 of IDS mailed on February 10, 2006), and Kim and Chandrasegaran (1994) PNAS 91: 883-887 (Reference CT of IDS mailed on February 13, 2004) that employ other DNA-binding domains such as GAL4 and homeobox type DNA binding domains. Cleavage domains have a similarly predictable and self-contained catalytic activity (e.g. type IIS restriction endonucleases, homing endonucleases, and topoisomerases). Accordingly, Applicants believe that it would not require undue experimentation for one of skill in the art to construct and use any chimeric nuclease comprising a DNA binding domain and a cleavage domain and, therefore, the claims are fully enabled throughout their scope.

The claims were also rejected for lack of enablement because it was alleged that the specification does not teach the presence of a nuclear localization signal in the claimed chimeric nucleases. The Examiner states "[i]t is not seen where in the specification it is taught that a nuclear localization signal is present in the chimeric nucleases made" (page 3, lines 13 and 14 of the office action). The Applicants respectfully disagree and note that this topic was discussed in

the interview of January 24, 2006. The specification teaches chimeric nucleases with nuclear localization signals and provides examples of such nucleases. For example, in the legend to Figure 3 (beginning at page 15, line 27), it is stated that "[e]ach [of the chimeric nucleases] have a standard initiation codon "ATG" followed by a nuclear localization signal, "N," at the amino terminus." Figure 3A provides a schematic diagram of the location of the nuclear localization signal in an exemplary construct encoding a chimeric nuclease. Additional descriptions of chimeric nucleases with nuclear localization signals are provided on page 48, line 6: "Applicants designed three different chimeric nucleases, each driven by the CMV promoter and containing a nuclear localization signal at their amino-termini (Figure 3A)." Nuclear localization signals (denoted by "NLS") are also included in the diagrams of Figures 5, 7, and 10 which show the structures of additional exemplary chimeric nucleases. Examples of nuclear localization signals that may be used are cited by reference and are stated to include "...any NLS [nuclear localization signal]....so long as the NLS is one that is compatible with the target organism" (page 23, lines 1-3). Thus the Applicants unambiguously teach the presence of a nuclear localization signal in a chimeric nuclease.

The Examiner has called attention to an error on page 55 wherein the Applicants have incorrectly referred to the chimeric nucleases shown in Figure 13. Applicants have amended the specification to correct the mistake.

In conclusion, the specification fully enables the construction and use of chimeric nucleases comprising nuclear localization signals as well as a number of DNA-binding and cleavage domains, and demonstrates their activity in gene targeting applications. Applicants therefore respectfully request reconsideration of the enablement rejections under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 112, first paragraph, written description

The Examiner has rejected claims 1-11, 13, 18, 20-21, 28, 40, and 98-123 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement because these claims supposedly contain subject matter "which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

The Applicants respectfully traverse. The Examiner claims again that "the instant specification apparently does not teach that a chimeric nuclease has been made with a nuclear localization signal." However, as established above, Figures 3, 5, 7, and 10 all depict structures of chimeric nucleases each containing a nuclear localization signal, and such nuclear localization signals are further described in the text (pages 15, 22-23, and 48, for example).

Applicants request that the Examiner reconsider the written description rejection under 35 U.S.C. § 112, first paragraph.

35 U.S.C. §103(a)

The Examiner rejects claims 43, 109-117 and 119-123 under 35 U.S.C. § 103(a) as being unpatentable over Bibikova, et al. (CA) in view of Choulika et al. (BD). Bibikova et al. are stated to teach the use of chimeric nucleases (Office Action at page 5) and Choulika et al. are stated to disclose essentially the method of claim 43 using a restriction enzyme instead of a chimeric nuclease (Office Action at page 6). The Examiner argues that the subject matter of the aforementioned claims would have been obvious to one of ordinary skill in the art in view of Bibikova et al. and Choulika et al.

Applicants respectfully traverse this rejection for reasons of record, inasmuch as Bibikova et al. fail to disclose or suggest (1) alteration of a sequence within genomic DNA or (2) use of a nuclear localization signal in a chimeric nuclease. *See* Response dated August 19, 2005 at pages 11-13. Nonetheless, and without conceding the correctness of the Examiner's position, but solely in order to expedite prosecution, claim 43 is amended to recite a nuclear localization signal. Inasmuch as this amendment renders claim 43 parallel to former claim 118, which was determined to be free of the art, Applicants believe the rejection has been overcome.

With respect to Choulika et al (BD), Applicants note that this reference, like Bibikova et al., fails to teach or suggest the use of a nuclear localization signal in a chimeric nuclease. Applicants also note that neither of US 2002/0110898 (Reference AS of IDS mailed on February 13, 2004) or US 2003/0229039, both of whose disclosures are cumulative to that of Choulika (BD), teach or suggest a chimeric nuclease comprising a nuclear localization signal.

Applicants also wish to mention the following additional related disclosures by Choulika: WO 00/46386 (Reference BE of IDS mailed on February 13, 2004), US 2002/0107214 (Reference AR of IDS mailed on February 13, 2004) and US 2004/0019002 (Reference A6 of IDS mailed on February 10, 2006); all of which are cumulative to one another and all of which fail to teach or suggest the use of a nuclear localization signal in a chimeric nuclease.

For the above reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

Conclusion

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to Deposit Account No. 18-1945, under Order No. CTCH-P01-016 from which the undersigned is authorized to draw.

Dated: February 10, 2006

Respectfully submitted,

By _____

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